Second-Line Treatment of Advanced Urothelial Cancer with Paclitaxel and Everolimus in a German Phase II Trial (AUO Trial AB 35/09)

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Abstract: OBJECTIVE: The efficacy of second-line treatment after failure of platinum-based chemotherapy in patients with advanced urothelial cancer is limited. Based on encouraging preclinical and clinical phase I data, we evaluated the safety and efficacy of the combination of paclitaxel and everolimus in these patients. METHODS: In this trial, patients having failed to respond to prior platinum-based combination treatment of urothelial cancer were treated with paclitaxel (175 mg/m(2) i.v., 3-weekly) and the mTOR-inhibitor everolimus (10 mg p.o., once daily). The patients were treated until tumor progression or until a maximum of 6 cycles was completed. A one-stage design was used to evaluate the objective response rate (ORR) as the primary endpoint. RESULTS: A total of 27 patients (67% male; median age 63 years) were enrolled. The most frequent grade III/IV toxicities were anemia (28%), peripheral neuropathy (28%), and fatigue (24%). No treatment-related deaths were reported. Complete and partial remissions were observed in 0/24 and 3/24 patients eligible for efficacy analysis, respectively (ORR 13%). Progression-free survival was 2.9 months [95% confidence interval (95% CI) 1.9-4.2], and the median overall survival was 5.6 months (95% CI 4.8-10.2). CONCLUSION: The combination of paclitaxel and everolimus has not achieved the expected efficacy in second-line treatment of urothelial cancer and should not be further explored.

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Key Words
Urothelial cancer · Chemotherapy · Platinum failure · Paclitaxel · Everolimus

Abstract
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Introduction

Cisplatin-based combination chemotherapy has emerged as a standard up-front treatment of metastatic or advanced urothelial cancer within the last decades. The regimens most frequently applied are gemcitabine/cisplatin, methotrexate/vinblastine/Adriamycin/cisplatin (MVAC), or dose-dense MVAC. The outcome of these

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combinations is comparable, resulting in an objective response rate (ORR) of 50–60%, a median progression-free survival (PFS) of 8–10 months, and a median overall survival (OS) of 14–16 months [1, 2]. In patients who are ineligible for cisplatin-based treatment regimens (e.g. due to impaired renal function or reduced performance status), a carboplatin-based combination treatment such as gemcitabine/carboplatin or methotrexate/carboplatin/vinblastine is the treatment of choice. However, this approach results in worse outcomes as compared to cisplatin-based treatment strategies [3].

After first-line treatment, a long-term response is observed in <20% of patients, and relapse or progression occurs within the first 3 years [1]. Subsequent second-line treatments are currently ill specified, and no accepted standard regimen has been defined. Recommended therapeutic options apart from clinical studies include reinduction of cisplatin-based treatment in patients who had a relapse-free interval of 6 months or longer, or treatment with vinflunine. However, vinflunine has been approved only in Europe for second-line treatment of urothelial cancer after platinum failure [4].

An alternative second-line treatment approach might be the use of paclitaxel. Compared to vinflunine (ORR 8.6%, PFS 3.0 months, OS 6.9 months), both paclitaxel monotherapy and paclitaxel-based combination treatment have been observed to provide acceptable treatment efficacies (ORR 9–42%, PFS 2.2–5.5 months, OS 6.9–8.0 months) [4–7].

In preclinical models, the efficacy of paclitaxel could be increased by the addition of everolimus [8]. Everolimus is an inhibitor of the PI3K/pAkt pathway targeting the serine/threonine kinase mTOR [9]. This inhibitor is approved for the treatment of several metastatic tumors, e.g. renal cell carcinoma, breast cancer, and neuroendocrine pancreatic cancer. The tolerability and safety of everolimus in combination with paclitaxel have been tested in two phase I trials in solid tumors [10, 11].

The aim of this phase II trial was to investigate the efficacy and safety of a combination therapy with paclitaxel and everolimus in patients with platinum-refractory metastatic urothelial cancer.

Subjects and Methods

Population

Eligible patients suffered from urothelial cancer of the upper or lower urinary tract and had failed to respond to prior platinum-based combination chemotherapy including palliative, neoadjuvant, and adjuvant treatment regimens. Other inclusion criteria were Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2, ≥1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST v1.0), and prior treatment with up to 4 chemotherapeutic drugs [12]. The main exclusion criteria were the presence of a predominant histology other than urothelial carcinoma and prior treatment with mTOR inhibitors or taxanes. Patients progressing within 3 months after neoadjuvant or adjuvant treatment were not eligible. The study protocol (CRAD001LDE17T, NCT00933374) was approved by the Ethics Committee at the Medical Faculty of the Heinrich Heine University, Düsseldorf, Germany. The protocol was followed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Assessments

Prior to the start of treatment, the patients were assessed for their medical and oncological history and ECOG PS [13]. In addition, an evaluation of hematologic and biochemical parameters, urinalysis, electrocardiography, and a physical examination including neurologic status were conducted. Tumor response and disease progression were measured at the baseline evaluation and at every other cycle every 6 weeks using the same imaging modality. Tumor response was assessed according to the RECIST v1.0 [12]. Toxicity and adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute version 3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf). The patients' reported quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) at baseline as well as at the beginning of each new treatment cycle [14].

Treatment Plan

Eligible patients received paclitaxel (175 mg/m^2 i.v.) 3-weekly and everolimus (10 mg p.o.) daily as a continuous treatment. They were treated either until disease progression as defined by the RECIST, until clinical disease progression, or until a maximum of 6 cycles was reached. Treatment with everolimus was discontinued in case of grade IV nonhematologic toxicity, grade IV thrombopenia, and grade IV febrile neutropenia. In case of dose-limiting grade III toxicities (DLT), everolimus was reduced after recovery (CTCAE grade ≤I) to 5 mg daily. If further DLT occurred, a reduction of the everolimus dose to 5 mg every other day was possible. Every further DLT led to a discontinuation of everolimus treatment. The paclitaxel dose was reduced by 20% (to 140 mg/m^2) for grade III/IV nonhematologic toxicity, grade III/IV febrile neutropenia, grade IV neutropenia, or grade IV thrombopenia only if the everolimus dose had already been reduced once or been discontinued. In case of grade III/IV neuropathy, the paclitaxel dose was reduced independently from the everolimus dose adaptions. A delay of treatment of >21 days resulted in exclusion from the trial.

Objectives

The primary objective was the ORR. Objective response was defined as either confirmed complete (CR) or confirmed partial remission (PR) as defined by the RECIST. ORR were analyzed in all patients having a relative dose intensity of ≥50% during the first 2 cycles.

The secondary objectives were OS, PFS, toxicity of combined treatment with paclitaxel and everolimus, and patients' reported quality of life. OS, PFS, and patient-reported quality of life were analyzed in all patients included in this trial. Toxicities were analyzed in all patients who received ≥1 dose of paclitaxel and/or everolimus.

Statistics

This was a single-arm multicenter phase II trial. A one-stage design was used to evaluate the response rate. An ORR <20% was defined as ineffective (null hypothesis), an ORR ≥40% was defined as effective (alternative hypothesis), assuming a higher efficacy of the combinatory treatment compared to paclitaxel monotherapy [7, 15]. To reject the null hypothesis, ≥7 objective responses (CR, PR) were required to be detected in 24 eligible patients ($\alpha = 10\%$, $\beta = 80\%$). Assuming a dropout rate of 20%, 30 patients were planned to be included in this trial.

The Kaplan-Meier product limit method was used to describe OS and PFS [medians, 95% confidence intervals (95% CI), and plots]. The OS and PFS of patients who did not have an event or receive any further anticancer therapy were censored at the date of the last adequate tumor assessment.

Endpoints for the analyses of patient-reported outcomes were the global health status/quality-of-life scale scores as well as the functioning scales of the EORTC QLQ-C30. The analysis comprised a repeated measurement analysis of these scales for patients with ≥1 postbaseline scale score. For statistical evaluation, a two-way analysis of variance including Bonferroni's posttest was used.

The assessment of safety was based on the frequency of adverse events and on the number of laboratory values that fell outside of predetermined ranges. After inclusion of the first 6 patients, an interim analysis regarding DLT was conducted. Statistical analyses were conducted using R version 3.0.2 and GraphPad Prism version 5.01.

Results

Patient Characteristics

Between July 2009 and December 2011, 27 patients were accrued for this trial. The patients' baseline characteristics are detailed in table 1. All 27 patients were eligible for survival analysis (OS, PFS).

Data on 24 patients were included in the efficacy analysis. Three patients were excluded as they received a <50% dose of treatment during the first 2 cycles. Two of them withdrew informed consent (1 patient before and 1 patient during the first cycle), and the third one needed to stop treatment before starting the second cycle due to herpes zoster which did not resolve within 21 days after discontinuation of the study treatment.

The safety analysis included 25 patients who had received ≥1 dose of either paclitaxel or everolimus. Both patients who withdrew informed consent were not eligible for the safety analysis.

Table 1. Patient and clinical baseline characteristics

Median age (range), years	63 (35–76)
Male:female ratio	18:9
Location of primary tumor	
Lower urinary tract/bladder	16
Upper urinary tract	8
Both	3
Treatment	
Surgical treatment of primary tumor	22
Ureterectomy, cystectomy	15
Nephrectomy, ureterectomy, nephroureterectomy	7
Biopsy/TURB only	5
Tumor grade (WHO 2004) at diagnosis	
High grade	19
Low grade	2
Missing	6
ECOG PS	
0	16
1	8
2	3
Bellmunt risk factors	
0	9
1	7
2	5
3	6
Location of metastases	
Liver	13
Lung	11
Bone	9
Lymph nodes	18
Other (including local recurrences)	7
Multiple sites	22
Prior treatment regimen	
Gemcitabine/cisplatin	21
Gemcitabine/carboplatin	2
Other	4
>1 line of treatment	4
Intention of prior platinum-based treatment	
Palliative	20
Perioperative	7

Values are numbers unless specified otherwise. Bellmunt risk factors were evaluated as described previously [22]. TURB = Transurethral resection and biopsy.

Efficacy and Survival

The ORR in the 24 evaluable patients was 12.5%, with 3 patients having a confirmed PR according to the RECIST. No CR was observed. Since based on the one-stage design ≥7 objective responses were required to be detected in the

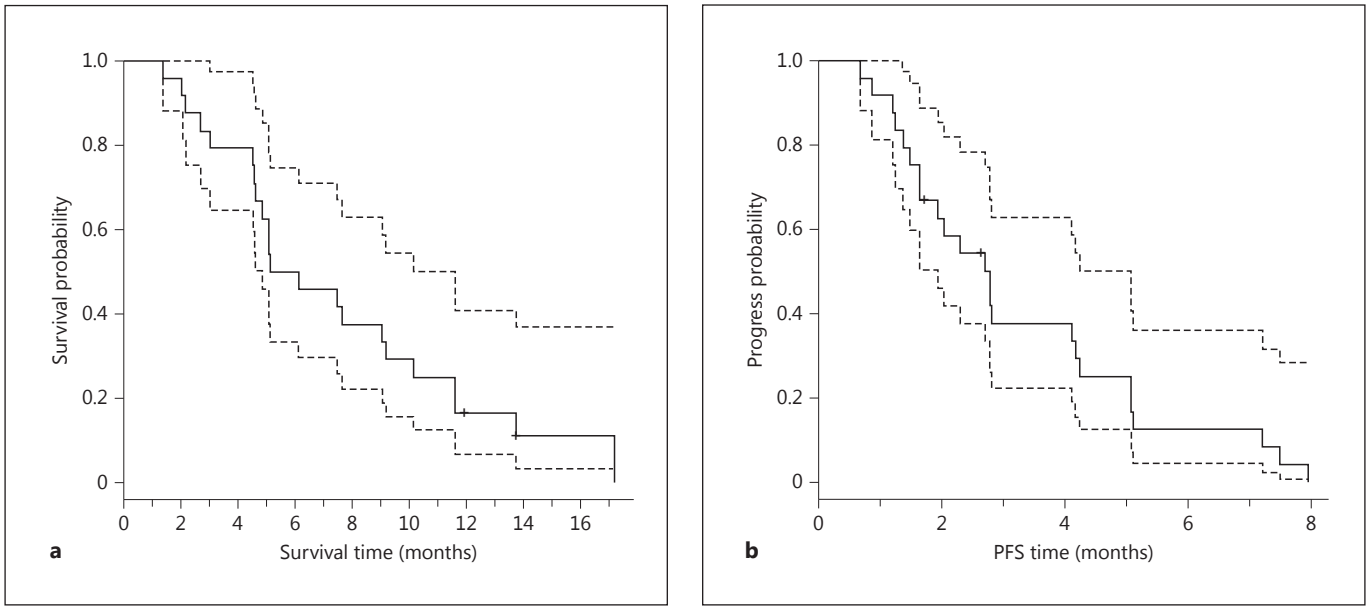

Fig. 1. OS and PFS in patients included in the efficacy analysis (n = 24). The Kaplan-Meier product limit method was used to describe OS and PFS. The Kaplan-Meier estimates are detailed as continuous lines, the 95% CIs as dotted lines. **a** The median OS was 5.6 months (95% CI 4.8–10.2). **b** The median PFS was 2.9 months (95% CI 1.9–4.2).

Table 2. Comparison of responders and nonresponders

	Responders (patient ID)			All other patients
	4003	6004	7004	
PFS, months	4.2	7.8	5.0	2.6[a]
OS, months	7.4	11.5	10.0	5.0[a]
Gender	f	f	f	6 f/15 m
Age, years	54	71	73	63[b]
1st-line setting	Peri	Met	Peri	8/21 Peri
Bellmunt risk factors, n	1	0	2	1[b]
ECOG PS	0	0	1	1[b]
Hb at baseline, g/dl	13.5	13.1	10.6	11.7[b]
Hepatic metastases	yes	no	yes	9/21
Localization of primary tumor	LT	UT	UT	LT: 12/21 UT: 9/21

f = Female; m = male; Peri = perioperative 1st-line chemotherapy; Met = 1st-line chemotherapy for metastatic disease; LT = lower tract; UT = upper tract. [a] Median value obtained by Kaplan-Meier analysis. [b] Median value.

24 patients to assume an superior efficacy of the combination over paclitaxel monotherapy, the primary endpoint was not met. Stable disease (including 2 unconfirmed responses) was observed in 11 patients (45.8%), and progressive disease in 10 (41.7%). The duration of response and OS in the 3 PR patients were 1.8, 3.3, and 5.3 months and 7.4, 11.0, and 10.0 months, respectively.

Median OS and PFS were 5.6 months (95% CI 4.8–10.2) and 2.9 months (95% CI 1.9–4.2), respectively (fig. 1). OS in patients with disease stabilization (PR/stable disease) was not different from that in PR patients. In all, 22/24 patients died during the treatment or within the 12-month follow-up period after termination of treatment.

In an additional exploratory analysis, no specific clinical characteristics discriminating responders and nonresponders could be identified (table 2). PFS in patients with lower urinary tract urothelial cancer was shorter compared to that in patients with upper urinary tract urothelial cancer, while OS and RECIST response were not different.

Safety

Overall, 95 treatment cycles were administered. The median number of treatment cycles was 4 (range 1–6, interquartile range 4). During the trial, 420 adverse events occurred in 25 patients. Grade III and grade IV toxicities were observed in 20 (80%) and 16 (64%) of the 25 patients, respectively. The most frequent adverse events observed were hematologic disturbances (60%). Neutrope-

Table 3. Overview of grade III and IV adverse events

	Grade III	Grade IV	All grades
Hematological			
Anemia	6	7	15
Neutropenia/leukopenia	7	4	15
Thrombopenia	1	2	7
Pain	4	3	14
Fatigue	5	6	12
Neurological			
Peripheral sensory neuropathy	0	7	12
Dizziness	0	2	3
Skin			
Alopecia	0	5	9
Acne	0	1	4
Dry skin	1	0	1
Gastrointestinal			
Nausea/vomiting	2	2	8
Diarrhea	1	0	5
Constipation	0	1	4
Mucositis	1	0	3
Renal failure	4	1	4
Infections			
Urinary tract infection	2	2	4
Pneumonia	1	0	2
Sepsis	2	0	2
Biliary tract infection	1	0	1
Kidney infection	0	1	1
Pneumonitis	0	1	1
Disturbed laboratory parameters			
Elevated liver enzymes	1	4	4
Hypokalemia	1	0	2
Hypocalcemia	1	1	1
Hyponatremia	1	0	1
Hypothyroidism	0	1	1
Other			
Dyspnea	1	1	3
Thrombosis	0	2	3
Hypertension	0	1	2
Ascites	1	0	1
Testicular operation	1	0	1
Ureteric stenosis	1	1	1

Numbers of patients in which the according adverse events were observed are provided.

nia and anemia were reported in 15 patients (60%) each, thrombopenia in 7 patients (28%) (table 3). Further frequent adverse events were pain (56%), peripheral neuropathy (48%), and fatigue (48%).

Table 4. Listing of serious adverse events potentially related to the study medication with CTCAE grade and outcome (not assessed)

Patient ID	Description of SAE	CTCAE grade	Outcome
Probably related			
4005	urinary tract infection	4	unknown
4007	neutrophil count decreased	4	recovered/resolved
6003	general symptom	NA	recovered/resolved
Possibly related			
2003	atrial fibrillation	2	recovered/resolved
4005	hemoglobin decreased	3	recovered/resolved
7002	sepsis	3	recovered/resolved
7002	hemoglobin decreased	4	recovered/resolved
7002	pneumonia	3	recovered/resolved

NA = Not applicable.

Thirty-nine serious adverse event diagnoses were reported in 12 patients; 8 of them may be related to the study medication (3 probably and 5 possibly; see table 4). No treatment-related deaths were reported.

Patient-Reported Quality of Life

During treatment, a temporary decline in physical (maximal change of absolute score: –11 points) and role functioning (maximal change of absolute score: –21 points) was observed. However, neither differences between baseline and end-of-treatment status nor differences comparing statuses between treatment cycles were statistically significant. Global health status/quality of life as well as emotional, cognitive, and emotional functioning scales remained unchanged (fig. 2).

Discussion

The primary objective of this trial was to evaluate the efficacy of the combination of paclitaxel and everolimus in the treatment of patients suffering from advanced urothelial cancer after failure of up-front platinum-based treatment, mainly using cisplatin. An objective response as defined by the RECIST in ≥7 of the 24 eligible patients was required to assume a higher efficacy of the combinatory treatment compared to paclitaxel monotherapy [7, 15]. Accordingly, as only 3 confirmed PR were observed (ORR 12.5%), the trial result needs to be considered negative. Given reported response rates of 9–10% with a reg-

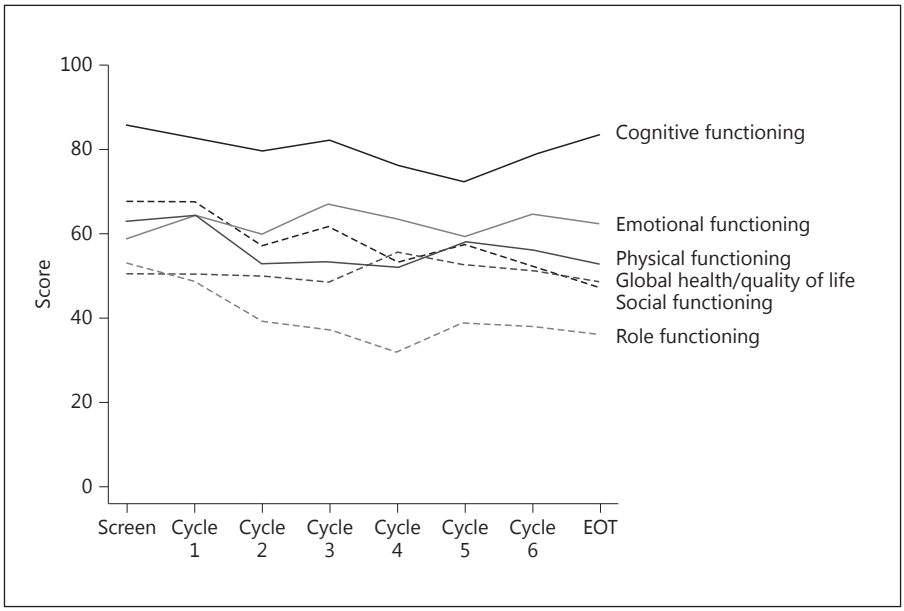

Fig. 2. Change in quality-of-life dimension scores with time. The various lines indicate the mean score values for the particular dimensions of the EORTC QLQ-C30. EOT = End of treatment.

imen of weekly paclitaxel (80 mg/m^2, d1, d8, d15, q4w), everolimus did not seem to add any clinical benefit to paclitaxel treatment in terms of response rate [7, 15].

However, progressive disease seemed to occur less frequently in our trial than reported from previous trials using paclitaxel monotherapy resulting in a disease control rate of nearly 60% [7]. Similar effects were recently observed in two trials using everolimus [16, 17] and in one trial using temsirolimus [18], another mTOR inhibitor, as monotherapy for urothelial cancer. Despite only marginal ORR, relevant disease control rates (27–51%) were likewise observed. Nevertheless, in spite of encouraging preclinical data showing synergistic effects by combining everolimus with paclitaxel, the results of our trial were below our expectations [8].

Typical everolimus-related toxicities (stomatitis, rash, fatigue, noninfectious pneumonitis) occurred in the expected range and were comparable to those observed in both trials investigating everolimus monotherapy for urothelial cancer [16, 17] as well as in a phase III trial evaluating everolimus as salvage treatment for metastatic renal cell carcinoma [19]. The frequency of typical paclitaxel-related adverse events, e.g. peripheral neuropathy, also did not seem to be increased [7]. In contrast, hematologic toxicities, especially neutropenia and anemia, were more frequent than has been reported for both paclitaxel and everolimus monotherapy [7, 16, 17, 19]. These findings are also in accordance with data from other trials investigating combination treatment with paclitaxel and everolimus [10, 20]. This suggests that cumulative bone marrow toxicity must be expected when these two compounds are combined, and this should be considered in further trials of combination treatment.

Concerning the quality-of-life analysis, our results are in line with the findings by other groups. For example, neither treatment with vinflunine nor treatment with paclitaxel after failure of up-front platinum-based treatment of urothelial cancer has been reported to impair patients' health-related quality of life (although significant toxicities were observed with both treatments and should have an impaired quality of life) [4, 7]. Merging quality-of-life data from the AUO trials AB 35/09 (paclitaxel + everolimus) and 20/99 (gemcitabine + paclitaxel), we have recently confirmed these results as well [21]. In cisplatin-based first-line treatment, von der Maase et al. [22] observed a stable health-related quality of life in patients undergoing treatment with either MVAC or gemcitabine/cisplatin, with no differences between the two patient groups. For the second large phase III trial of up-front treatment for urothelial cancer comparing MVAC to high-dose-intensity MVAC, no data on health-related quality of life have been reported [23].

In our trial, the PFS of patients undergoing treatment with paclitaxel and everolimus was comparable to that with other taxane-based treatment regimens as well as monotherapy with vinflunine (2.2–5.5 months). However, the OS of 5.6 months was lower than that reported in these trials (6.9–8.0 months) [4, 7, 15, 24]. As an initial

response to treatment with disease stabilization was observed in more than half of the patients and no treatment-related deaths were reported, this finding might be attributable to the poor prognostic factors observed in our cohort rather than to the efficacy of the treatment regimen. About three quarters of the patients in this trial suffered from visceral metastases (74%), and >80% had multiorgan involvement. In comparison, visceral metastases and multiorgan involvement were less frequent in the largest trial of paclitaxel monotherapy (58 and 67%, respectively) and in a phase III trial comparing short-term and long-term combinatorial treatment with paclitaxel and gemcitabine (38 and 46%, respectively) [7, 25, 26]. In addition, 41% of the patients presented with 2 or 3 poor prognostic factors (Hb ≤10 g/dl, liver metastases, ECOG PS ≥1) compared to 33 and 23% in the vinflunine phase III and the gemcitabine/paclitaxel trial, respectively [25, 26].

Despite initial enthusiasm regarding inhibition of the PI3K/Akt/mTOR signaling pathway as a suitable targeted approach in urothelial cancer, it must be concluded from 4 recent phase II trials that the clinical efficacy of mTOR inhibitors in this disease has been modest at best [16–18]. This is surprising, given the recent finding of mutations (both activating and inactivating) of several key enzymes of PI3K/Akt/mTOR signaling by the Cancer Genome Atlas project in a number of cases [27]. Interestingly, an activity of mTOR inhibitors has been reported in at least some urothelial cancer patients, given 3 PR and 1 CR after everolimus monotherapy as well as a relevant disease control rate in two phase II trials [16, 17]. This raises the question of how those patients who have the highest likelihood of experiencing benefits from the use of an mTOR inhibitor might be identified. Concomitant molecular investigations to resolve this issue have yielded inconsistent results in urothelial cancer. While in the trial by Seront et al. [16], an association between loss of PTEN and response to everolimus was suggested, Milowsky et al. [17] were not able to confirm this observation. An analysis of the tumor genome of 1 urothelial bladder cancer patient with CR after treatment with everolimus monotherapy revealed mutations in the *TSC1* gene, an upstream inhibitor of the mTOR signaling pathway [28]. Interestingly, an increased rate of *TSC1* mutations in patients with radiographic treatment response was also observed in a small validation cohort of patients in the same trial. Prospective validation is warranted to clarify whether this finding may help to identify patients who might benefit from mTOR inhibitors in the future.

An alternative explanation for the apparently low frequency of responders to mTOR inhibition might be the observation of an Akt-dependent, but mTOR-independent, regulation of 4EBP1 [29]. Accordingly, the use of inhibitors of upstream regulators of mTOR activity, i.e. targeting Akt itself, may be a more promising approach in patients in whom tumor progression is suspected to depend on PI3K/Akt/mTOR signaling.

Evaluating the results of our analysis, several flaws and limitations need to be considered. Certainly, the main points are the limited patient number and the long time frame for the recruitment of patients. One potential reason for this might have been the introduction of vinflunine on the market in Germany in 2009. Further potential reasons might have been the general reluctance of treating physicians to refer palliative patients who have failed up-front cisplatin-based treatment and generally present in a poor condition for further toxic treatment. However, this trial was primarily designed to detect a first efficacy signal as well as statistical measures to capture this signal, e.g. an α failure of 10% and a rather low target ORR of 20%.

In conclusion, the combination of paclitaxel and everolimus has failed to demonstrate the expected efficacy in second-line treatment of urothelial cancer. Apart from an increased number of hematologic adverse events, the toxicities were comparable to those observed with other second-line treatment options. Clinical factors for the prediction of treatment response remain elusive. Until predictive biomarkers will be available to guide the use of inhibitors targeting the PI3K/Akt/mTOR signaling pathway, mTOR inhibitors should not be further tested as a treatment option in an unselected population of patients with advanced urothelial cancer.

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Disclosure Statement

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